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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,698	03/30/2001	Hendricus R.J.M. Hoogenboom	DYX-015.1 US	5332

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/822,698	HOOGENBOOM ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 70-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3* is/are allowed.

6)☐ Claim(s) *1,2,4-29 and 70-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RE: Hoogenboom et al
Priority Date: 30 March 2000

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/2004 has been entered.

2. Claims 1-29 and 70-81 are pending and examined on the merits.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code (see for example page 36). The examiner has not gone through the entire specification to locate all hyperlinks, applicant is ask check and removed all embedded hyperlinks from the specification. See MPEP § 608.01.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

4. The rejection of claims 4-7 and 18-29 under 35 USC § 112, 1st paragraph as lacking written description is maintained for the reasons of record. Applicant argues

that the amendments to limit the claims to conservative substitutions to amino acids 99-110 of SEQ ID No: 3 would obviate the instant rejection. Specifically, applicant states that the examiner indicates that substitutions to SEQ ID No: 3 are adequately represented in the specification because page 56 teaches representative species of the genus. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

Applicant's amendments to the claims are not deemed sufficient to overcome the rejection of record because the specification has not specifically taught a representative genus of variants to represent the highly variant genus of peptides claimed. Specifically, the claims are still drawn to sequences that are not adequately defined or disclosed in the specification as filed. The specification specifically teaches several species of amino acid SEQ ID No: 3 (specifically between amino acids 99-110) as defined and identified in the specification on page 56 by a specific sequence identifier. However, the claims are still drawn to sequences that have not been defined in the specification. This case is analogous to example 13 of the Revised Interim Written description Guidelines (http://www.uspto.gov/web/offices/pac/writtendesc.pdf) where a genus of structurally variants proteins were deemed to lack written description because of the highly variant nature of the genus claimed and where structural differences existed between the members of the genus. As stated in the example and related to this case, structural features that could be use to distinguish the compounds of the genus from others in the protein class are missing the instant disclosure. No common core structure is provided so as to relate the specific species in the specification to other non disclosed variants.

The specification only provides general guidance in terms of what is encompassed by the variants claimed. However, specific, not general guidance is required to satisfy what is not known or taught in the art. Moreover, the instantly claimed genus is highly variable. For example, the instantly claimed polypeptides are defined as MUC-1 binding members, which differ from the specifically defined species (i.e. those that are described by an associated sequence identification number) due to a conservative substitution, or related by a specific percent homology. However, Wu X *et al* (Clin. Immunol. Immunopathol. 1998;87:184-192) teach an antibody that comprises a substitutions that at position 99 and falls within the scope of the claimed MUC-1 binding protein and yet it is an antibody that is specific for myosin. Thus, the written description for the MUC-1 binding members claimed has not been fully disclosed and has been found to be highly variable.

Therefore, the written description rejection is maintained for the reasons of record and therefore the claims are still rejected under 35 USC 112, 1st paragraph as lacking written description.

New Arguments

Claim Rejections - 35 USC § 112, 2nd paragraph

5. Claims 1-2,4-14, and 75-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the claims recite "its germ line" as part of the invention, however, it is unclear as to what germ line is specifically being referred. Moreover, certain claims also refer to "a framework from a different germ line", however, because the claims have not specifically taught which germ line is encompassed, one of skill cannot determine of the germ line is in fact different. Therefore, the metes and bounds cannot be adequately determined because one of skill cannot determine which germ line is being claimed.

Claim Rejections - 35 USC § 101

6. Claims 24-29, and 80-81, as written, do not sufficiently distinguish over proteins, as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to include the term "isolated" as disclosed on page 3 of the specification.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 1-2,4-29, and 70-81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a MUC-1 antigen binding fragment comprising three CDR regions from SEQ ID No: 1 and 3 in the DP47 and DPK15 framework, does not reasonably provide enablement for a MUC-1 specific binding member comprising less than three CDR regions in any and all generic framework

regions or germ line framework regions claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQZd 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a MUC-1 specific binding member comprising the an amino acid sequence of the formula of SEQ ID No: 28. The claims are also drawn to a MUC-1 specific binding member that comprises a CDR region from SEQ ID Nos.: 1 or 3 and homologues that are between 70%-99% homologous. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims read broadly on a MUC-1 specific binding member that consists of a single CDR regions from SEQ ID Nos.: 1 and or 3 wherein the member can be peptides, antibodies or antibody fragments.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since there is significant variability between the binding specificities associated with each CDR region combination that makes up the binding pocket of an antibody. Moreover, the addition of conservative substitutions to a binding pocket alters the binding characteristics of the CDRs and therefore changes its specificities. It would therefore require significant study to identify which substitutions, and which CDRs are required for specific binding specificity, and the identification of these regions would in itself be inventive and unpredictable with no reasonable expectation of success. This would require years of invention effort , with each of the many intervening steps not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable

regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff *et al* (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff *et al* teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Moreover, Panka *et al* (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substiution of serine for alanine results in decreased affinity. Also, in at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Working examples

The specification teaches the isolation and characterization of MUC-1 antigen binding regions of SEQ ID No: 1 DPK15 germ line and SEQ ID No: 3 from DP47 germ line. The specification also teaches numerous variants of a CDR region of SEQ ID No: 3 (see page 56).

Guidance in the specification

It is unlikely that a MUC-1 binding member of a single CDR as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of a MUC-1 antibody in unspecified order and fused to any human or nonhuman framework sequence, would have the required binding function. Moreover, the specification has not provided a peptide that is capable of binding to

MUC-1 that is not the full variable region (i.e. all three CDR regions) of SEQ ID No: 1 or 3. In addition, the specification has also not provided any other germ line framework regions with the given SEQ ID No: 1 or 3 that retains MUC-1 binding specificity. Therefore the guidance in the specification is essentially limited to peptides or antigen binding regions that comprise the full sequence of SEQ ID No: 1 or 3 that is capable of binding to MUC-1 within the DPK15 and or DP47 germ line framework.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 12/16/2004.

Conclusion

Claim 3 is allowed. Claims 1-2,4-29, and 70-81 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
March 15, 2005

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
3/17/05